Nephrogenic Diabetes Insipidus as the First Manifestation of Ectopic ACTH Syndrome in a HIV Infected Patient

CASE REPORT

Everlayny Fiorot Costalonga¹, Amanda Weberling Coelho Moreira²,
Francisca Germany Moraes Borges², Veronica Gabriela Guerra³, Thais Leibel Sant' Anna Santos²,
Leon Cleres Penido Pinheiro³, Susan Caroline Azevedo Aredes², Weverton Machado Luchi⁴

Abstract

The Ectopic Adrenocorticotrophic Hormone (ACTH) Syndrome (EAS) is a high mortality paraneoplastic syndrome, which represents 10-15% of Cushing Syndromes (CS). Around 70% of tumors are located in the chest, neck or adrenals. It frequently has atypical manifestations, leading to delay in diagnosis. Here, we report a particular case of EAS manifested predominantly by nephrogenic diabetes insipidus (NDI). A 48 years old man, HIV infected, was admitted with polyuria, polydipsia and lower limb weakness. He had hypertension, crackles in the right hemithorax and lymphadenopathy. Laboratory assessments showed hyperglycemia, hyponatremia, severe hypocalcemia, metabolic alkalosis and low urinary osmolality, which persisted after water deprivation test and desmopressin administration, characterizing a NDI. Chest images showed a lung tumor, which, in conjunction with the clinical and laboratory picture lead to the suspicion of EAS. Cortisol levels after dexamethasone were 143µg/dL and serum ACTH was 630pg/mL. Pituitary was normal and adrenals showed bilateral hyperplasia. Lymph node biopsy revealed a neuroendocrine tumor with positive immunohistochemistry for ACTH. Patient died a few days later due to nosocomial pneumonia. The EAS can be associated with very high cortisol levels, which evolves rapidly, resulting in the absence of typical features of CS. The knowledge of the different clinical presentations is essential to establish prompt diagnostic and support. This syndrome has to be considered in patients with a neoplasm and diabetes insipidus, especially if accompanied by signs of excess of mineralocorticoid action. Although the ideal treatment is excision of the tumor, adrenolytic drugs may help to reduce complications and improve survival.

- 1 PhD in Endocrinology, Professor of the Department of Clinical Medicine of Federal University of Espírito Santo, Vitória, ES, Brazil.
- 2 Medical Resident in Internal Medicine, Federal University of Espírito Santo, Vitória, ES, Brazil.
- 3 Graduating Medical Student, of Federal University of Espírito Santo, Vitória, ES, Brazil.
- 4 PhD in Nephrology, Professor of the Department of Clinical Medicine of Federal University of Espírito Santo, Vitória, ES, Brazil.

Contact information:

Everlayny Fiorot Costalonga.

Address: R. Tupinambás, 342, apto 504, Jardim da Penha, Vitória, ES, Brasil. CEP 29060-810.

everlayny@gmail.com

Keywords

Ectopic ACTH Syndrome;
Cushing Syndrome; Diabetes
Insipidus; Lung Neoplasms;
HIV Infection.

Introduction

The Ectopic Adrenocorticotrophic Hormone (ACTH) Syndrome (EAS) is a high mortality paraneoplastic condition characterized by a severe hypercortisolism state induced by ectopic secretion of ACTH. It represents around 20% of ACTH-dependent and 10% of all types of Cushing's Syndrome (CS) [1, 2].

More than a half of tumors are located in the lungs or thymus and 70% can be found in the chest, neck or adrenals. The most frequent tumors involved are small cell lung carcinoma, carcinoid tumors of the lung, thymus and pancreas, medullary thyroid carcinoma, pancreatic islet cell and pheochromocytoma. Nevertheless, in 12-37.5% of cases, the source of ectopic ACTH secretion remains unknown [1-3].

The clinical presentation is heterogeneous and appears to be related to the degree of hypercortisolism, varying from typical CS symptoms and signs (such as central obesity, moon-like face and violaceous striae) to an unusual or atypical picture with aldosterone-like effects, psychiatric manifestations, weight loss, polyuria, skin pigmentation, ankle edema, osteoporosis, aortic dissection and infections [1, 2, 4-7].

The state of severe hypercortisolism is responsible for important metabolic and cardiovascular complications, contributing to reduce the quality-of-life and to increased mortality, beyond the oncologic outcomes [7]. Thereby, the knowledge of the different clinical presentations of this syndrome is important to establish a prompt diagnostic and provide an adequate clinical support to these patients.

In this article, we describe a case of EAS associated to lung cancer in a HIV infected man, in which the initial manifestation was polyuria and polydipsia secondary to Diabetes Insipidus (DI). Very few cases of DI have been reported in association with EAS, and most of them were linked to intrasellar metastasis of the primary ACTH – producing tumor [4]. In this case, diluted polyuria persisted after vasopressin administration and pituitary image did not show in-

filtrative lesions, indicating a nephrogenic form of DI, which is a frequently unknown or forgotten manifestation of severe hypercortisolism.

Case Report

Admission

A 48-year-old man, caucasian, smoker for 22 years (1 pack a day), diagnosed with HIV five years ago, regularly using efavirenz, tenofovir and lamivudine, with suppressed viral load and CD4 count of 711 cells/mm³, was admitted for the evaluation of a 3-week history of abrupt onset of severe polyuria, polydipsia, nocturia and lower limb weakness. After inquiring, the patient complained of a frequent productive cough in the last month, without fever, sweats, chills or weight loss. There was no previous medical history of kidney disease, hypertension or diabetes mellitus.

On admission, he was 175 cm high, and weighted 61 Kg (body mass index of 20 kg/m²), appeared well-hydrated, ruddy, anicteric, acyanotic, eupneic and afebrile. There was a mild facial and bilateral ankle edema, normal distribution of fatty tissue and no skin abnormalities, such as striae or hyperpigmentation and right axillary and supraclavicular lymph node of 2cm. Cardiovascular examination showed high blood pressure (160/100 mmHg) and lung auscultation revealed sparse crackles and wheezing in the right hemithorax. Abdominal examination was unremarkable and neurological analysis displayed proximal and distal weakness (3/5) of lower limbs musculature with discrete hypotrophy.

Initial laboratory assessments (**Table 1** and **2**) showed severe hypokalemia and metabolic alkalosis, hypernatremia, high blood glucose, normal urinary chloride, high serum osmolality, low urinary density and mild glycosuria. Chest radiograph showed a nodular opacity image at the level of the middle third of the right lung (**Figure 1A**).

Table 1. Admission Serum Values.

Parameters	Values	Reference
Creatinine	0.65	0.7 – 1.2 mg/dL
Urea	25	10 – 50 mg/dL
Ionized calcium	4.5	4.49 – 5.29 mmol/L
Chloride	106	98 – 106 mEq/L
Phosphorus	3.6	2.5 – 4.9 mg/dL
Magnesium	1.94	1.8 – 2.4 mg/dL
Potassium	1.91	3.5 – 5.1 mEq/L
Sodium	150	134 – 146 mEq/L
Glycemia	151	70 – 99 mg/dL
Hemoglobin	16.3	13 – 17 g/dL
White blood cell count	13.25	5 – 10 k/uL
LDH	902	200 – 480 U/L
Uric acid	2.59	2.6 – 7.2 mg/dL
Arterial blood pH	7.536	7.35 – 7.45
Bicarbonate	34.7	22 – 26mmol/L
Arterial PCO2	44	35 – 40 mmHg
Osmolality	300	285 – 290mOsm/kg

Table 2. Urinary values.

Parameters	Admission (Urinalysis)	Week 2 24h urine (volume = 8.6Liters)	Reference
pH	8	7	4.5 – 8
Density	1.009	1.005	1.005 – 1.030
Glucose	300mg/dL	negative	< 10mg/dL
Osmolality		240	50 – 1200 Osm/Kg
Sodium		57	20 – 110 mmol/L
Chloride		84	55 – 125 mmol/L
Potassium			
Concentration		31 mmol/L	12 – 62 mmol/L
24h K Excretion		263 mmol	25 – 136 mmol/24h
FE* (%)		33	4 – 16%
TTKG#		10	4 – 6

*: Fraction of excretion; #: Transtubular potassium transport.

Figure 1: A) Chest radiograph showed a nodular opacity image on 1/3 medium in the right lung. B) CT image showing pulmonary spiculated nodule of 2,2 cm in the right upper lobe.

Follow-up and clinical diagnosis

During hospital internment, urinary output ranged from 6 to 9 liters, despite of serum glucose control and absence of glycosuria, excluding the possibility of polyuria to be secondary to glycosuria. Plasma osmolality mostly remained above 295 mOsm/L and urinary osmolality around 240 mOsm/L. During a water deprivation test and intranasal vasopressin administration, the urine density remained persistently low and the sodium serum levels increased,

Figure 2: A) Water deprivation test. Solid and dashed lines represent plasma sodium (PNa) and urinary density, respectively. Increase of PNa and persistent low urine density/osmolality after water deprivation, even with desmopressin (DDAVP) administration, indicating nephrogenic diabetes insipidus. B) Absence of a correlation between urinary volume (UV) and plasma potassium levels (PK). Pearson correlation: $r=0.19$; $p=0.46$.

Figure 3: Abdominal CT images showing bilateral adrenal hyperplasia (black arrows).

consistent with the diagnosis of Nephrogenic Diabetes Insipidus (NDI) (**Figure 2A**).

Refractory renal hypokalemia (excretion fraction of 33% and transtubular potassium gradient of 10) was present in the most of the time despite of potassium intravenous replacement and 100 mg of spironolactone, questioning this causal factor on NDI. Nevertheless, we found no correlation between potassium levels and urinary volume (**Figure 2B**). The NDI secondary to tenofovir was also hypothesized, however, despite the discontinuation of this drug, the patient persisted with high daily diluted urine volume, as high as 6-8L/day.

In front of a renal hypokalemia associated with chloride-resistant metabolic alkalosis (urinary chloride of 84 mmol/L) and hypertension, excess of mineralocorticoids was evoked. Unfortunately, the dosage of aldosterone and renin was not possible. Nevertheless, abdominal computed tomography (CT) scan showed bilateral adrenal hyperplasia (**Figure 3**). The chest CT exhibited a pulmonary right spiculated nodule of 2.2 cm, in the right upper lobe, associated with mediastinal and hilar lymphadenopathy (**Figure 1B**). In face of this clinical, laboratory and radiological scenario, we hypothesized the possibility of ectopic ACTH secretion.

His baseline serum cortisol dosage was 63ug/ml (reference values: 6.2-19.4 ug/ml) and there was no suppression after low-dose dexamethasone test (1 mg overnight: 143µg/dL; 2mg 48h: 63 µg/dL). Magnetic resonance imaging (MRI) of sellar region were normal, except for the absence of the neu-

rophypophysis "bright spot", a signal indicative of vasopressin storage (**Figure 4**). Serum ACTH was 630pg/ml (reference values: 10 – 60 pg/mL). Supraclavicular lymph node biopsy revealed a high-grade neuroendocrine carcinoma (**Figure 5A**), with a positive immunohistochemistry for ACTH (**Figure 5B**), which confirmed our hypothesis. He was referred to an oncology center with the purpose of specific chemotherapy treatment, but died a few days later due to nosocomial pneumonia.

Figure 4: Sagittal T1-weighted MRI shows absent posterior pituitary hyperintensity known as "bright spot" (a signal indicative of vasopressin storage), normal stalk and anterior pituitary.

Discussion

Ectopic ACTH secretion is a rare manifestation of lung tumors, occurring in 3.2% to 4.5% of cases [4]. It often results in severe hypercortisolemia, which increases the already high morbimortality of the underlying condition. The higher the cortisolemia, the most atypical the manifestation, implying that high levels of perspicacity and knowledge of the possible clinical presentations are needed to establish a prompt diagnosis [1, 2]. Here, we presented a case of EAS in a HIV infected patient, manifested predominantly by NDI, metabolic alkalosis and hypocalcemia, which were mistakenly attributed to tenofovir nephrotoxicity and/or hypokalemia at first.

Figure 5: Supraclavicular lymph node biopsy: A) High-grade neuroendocrine carcinoma. B) positive immunohistochemistry for ACTH.

Even though the CS caused by EAS has been traditionally associated with atypical manifestations, such as ankle edema, psychiatric disorders and fractures, DI has rarely been included as a possible manifestation of severe hypercortisolemia. Most of the previous reports of the association between EAS and DI were related to the presence of pituitary metastases causing central DI [4], and only one report described a mixed central and nephrogenic DI [5]. Thus, to our knowledge, this is the first description of purely NDI caused by EAS.

Although frequently forgotten, the association between hypercortisolism and hypotonic polyuria is well established. The pathophysiological mechanisms linking this two endocrine disturbances includes: 1) suppression of vasopressin secretion by hypothalamic feedback action exerted by cortisol [7-9]; 2) antagonism of renal vasopressin action [10, 11]; and 3) impairment of vasopressin action mediated by severe hypokalemia [12, 1, 2, 13].

Hypokalemia, which is present in up to 70% of EAS cases, is a well-known cause of NDI, and is associated to cyclic AMP system inhibition and down-regulation of aquaporin-2 water channel expression in collecting ducts [13, 14]. However, in our case, we found no direct correlation between potassium levels and diuresis. In this scenario, previous studies suggest that polyuria linked to cortisol action is independent of hypokalemia [10, 15]. Besides, other studies have demonstrated that the polyuria is vasopressin resistant, indicating that the primarily involved mechanism is the reduction of water permeability in collecting ducts by impairment of ADH effect [12].

In this case, the diagnosis of EAS was delayed by the presence of comorbidities and the use of multiple drugs, which is a frequent problem in clinical practice. Although the patient had hypertension and hyperglycemia, which are typical finds of Cushing syndrome, those features were initially attributed to HIV infection and lipodystrophy induced by antiretroviral therapy. Hypokalemia and diabetes

insipidus, by the other side, were primarily ascribed to tenofovir nephrotoxicity.

Tenofovir is a frequently used antiretroviral drug which has been associated to a pattern of nephrotoxicity characterized mainly by proximal tubule disturbances, which include renal Fanconi syndrome and acute kidney injury in severe cases [16]. Although it can cause NDI in about 12.5% of cases, it is usually associated with kidney injury and metabolic acidosis, in contrast with our patient, who presented chloride resistant metabolic alkalosis and normal kidney function [17, 18].

In adults, the association of severe hypocalcemia, chloride resistant metabolic alkalosis and systemic hypertension must always lead to the hypothesis of excess of mineralocorticoid action. It can be caused by excess of aldosterone production (aldosteronomas, primary adrenal hyperplasia, adrenocortical carcinoma) or by excess of mineralocorticoid action exerted by other substances, such as 11-deoxycorticosterone (congenital adrenal hyperplasia) or cortisol (syndrome of apparent mineralocorticoid excess, glucocorticoid resistance and CS).

Although most of the effects of cortisol are mediated by the glucocorticoid receptor, cortisol can also bind to the mineralocorticoid receptor (MR). In physiological conditions, MR is protected from the action of cortisol by the conversion of cortisol to the inactive molecule cortisone, which is mediated by the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11BHSD2). In EAS, the extremely high ACTH and cortisol levels, such as those observed in this case, overwhelm inactivation of cortisol by the 11 β HSD2 enzyme on the MR; thus resulting in aldosterone-like effects of cortisol in the kidney [7]. For this reason, in patients with confirmed or suspected neoplasm, the presence of excess of mineralocorticoid action should promptly point to the suspicion of EAS.

Once made the suspicion, the confirmation of the diagnosis of EAS requires a rigorous and sequential complementary evaluation, that includes: 1) esta-

blishment of endogenous autonomous hypercortisolemia; 2) verification of ACTH dependency; 3) differentiation of the more common pituitary Cushing Disease; and 4) localization of the source of ACTH secretion [6, 7, 19]. In this patient, the presence of autonomous hypercortisolemia was confirmed by the absence of suppression of cortisol by dexametasone. The ACTH dependency was confirmed by the extremely high levels of morning serum ACTH. Cushing disease was excluded by absence of pituitary adenoma and by the confirmation of the source of ACTH secretion, demonstrated by the immunohistochemistry positivity for ACTH in the supraclavicular lymph node biopsy [1].

Tumors manifested by EAS have been associated with reduced survival despite appropriate treatment, possibly due to complications such as sepsis, aortic dissection and gastrointestinal haemorrhage [4, 20]. Although the ideal treatment is excision of the tumor, drugs that help to control the effects of hypercortisolemia are important tools to reduce some of these complications. One or more drugs can be used, including ketoconazole, etomidate, mitotane, mifepristone, dopamine agonists, or the somatostatin analogs [21-23]. Reports of response to multi-kinase inhibitors, such as sorafenib, have also been published [20]. In our patient, the delay of the diagnosis and the hasty evolution to sepsis impaired the establishment of any specific treatment on time.

Therefore, the case reported is an opportunity to alert clinicians for the possibility of NDI being the first manifestation of severe hypercortisolemia, such as the observed in EAS.

Conclusions

EAS is a high mortality paraneoplastic syndrome. More than a half of tumors are located in the lungs or thymus. It can present with unusual signs of hypercortisolism, such as hypocalcemia, metabolic alkalosis and central or nephrogenic DI. Tenofovir toxicity can cause NDI, but is associated with renal injury

and metabolic acidosis. The association of severe hypocalcemia, chloride resistant metabolic alkalosis and systemic hypertension suggests excess of mineralocorticoid action. In patients with confirmed or suspected neoplasm, the presence of excess of mineralocorticoid action should promptly point to the suspicion of EAS. The control the hypercortisolemia is important to reduce some of the complications and reduced survival rates of EAS.

Funding

None

Conflict Of Interest

The authors declare that they have no competing interests.

References

1. Alexandraki KI, Grossman AB. The ectopic ACTH syndrome. *Rev Endocr Metab Disord* 2010 Jun; 11(2):117-26.
2. Isidori AM, Lenzi A. Ectopic ACTH syndrome. *Arq Bras Endocrinol Metabol* 2007 Nov; 51(8):1217-25.
3. Salgado LF, MCBV; Knoepfelmacher,M; Machado, MC; Domenice,S; Pereira, MAA; Mendonca,BB. Ectopic ACTH syndrome: our experience with 25 cases. *European Journal of Endocrinology* 2006; 155.
4. Agha A, Brennan S, Moore KB, Grogan L, Thompson CJ. Small-cell lung cancer presenting as diabetes insipidus and Cushing's syndrome. *Pituitary* 2005; 8(2):105-7.
5. Lococo F, Negro A, Zanelli F, Valli R, Filice A, Rapicetta C, et al. Severe Cushing's syndrome related to a small pulmonary carcinoid with widespread dissemination. *Intern Med* 2015; 54(5):477-80.
6. Raff H. Cushing syndrome: update on testing. *Endocrinol Metab Clin North Am* 2015 Mar; 44(1):43-50.
7. Raff H, Carroll T. Cushing's syndrome: from physiological principles to diagnosis and clinical care. *J Physiol* 2014 Feb 1; 593(3):493-506.
8. Papanek PE, Raff H. Physiological increases in cortisol inhibit basal vasopressin release in conscious dogs. *Am J Physiol* 1994 Jun; 266(6 Pt 2):R1744-51.
9. Raff H. Glucocorticoid inhibition of neurohypophyseal vasopressin secretion. *Am J Physiol* 1987 Apr; 252(4 Pt 2):R635-44.
10. Baas JJ, Schaeffer F, Joles JA. The influence of cortisol excess on kidney function in the dog. *Vet Q* 1984 Jan; 6(1):17-21.

11. Joles JA, Rijnberk A, van den Brom WE, Dogterom J. Studies on the mechanism of polyuria induced by cortisol excess in the dog. *Vet Q* 1980 Oct; 2(4):199-205.
12. Giebisch G, Lozano R. The effects of adrenal steroids and potassium depletion on the elaboration of an osmotically concentrated urine. *J Clin Invest* 1959 May; 38(5):843-53.
13. Marples D, Frokiaer J, Dorup J, Knepper MA, Nielsen S. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. *J Clin Invest* 1996 Apr 15; 97(8):1960-8.
14. Kim JK, Summer SN, Berl T. The cyclic AMP system in the inner medullary collecting duct of the potassium-depleted rat. *Kidney Int* 1984 Oct; 26(4):384-91.
15. Raisz LG, McNeely WF, Saxon L, Rosenbaum JD. The effects of cortisone and hydrocortisone on water diuresis and renal function in man. *J Clin Invest* 1957 Jun; 36(6 Part 1):767-79.
16. Hall AM. Update on tenofovir toxicity in the kidney. *Pediatr Nephrol* 2013 Jul; 28(7):1011-23.
17. Zaidan M, Lescure FX, Brocheriou I, Dettwiler S, Guiard-Schmid JB, Pacanowski J, et al. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: a clinico-pathological study. *Clin J Am Soc Nephrol* 2013 Jun; 8(6):930-8.
18. Libório AB, Andrade L, Pereira LV, Sanches TR, Shimizu MH, Seguro AC. Rosiglitazone reverses tenofovir-induced nephrotoxicity. *Kidney Int* 2008 Oct; 74(7):910-8.
19. Newell-Price J, Grossman AB. Differential diagnosis of Cushing's syndrome. *Arq Bras Endocrinol Metabol* 2007 Nov; 51(8):1199-206.
20. Hammami MM, Duaiji N, Mutairi G, Aklabi S, Qattan N, Abouzied Mel D, et al. Case report of severe Cushing's syndrome in medullary thyroid cancer complicated by functional diabetes insipidus, aortic dissection, jejunal intussusception, and paraneoplastic dysautonomia: remission with sorafenib without reduction in cortisol concentration. *BMC Cancer* 2015; 15:624.
21. Cuevas-Ramos D, Fleseriu M. Treatment of Cushing's disease: a mechanistic update. *J Endocrinol* 2014 Nov; 223(2):R19-39.
22. Feelders RA, Hofland LJ. Medical treatment of Cushing's disease. *J Clin Endocrinol Metab* 2013 Feb; 98(2):425-38.
23. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015 Aug; 100(8):2807-31.

Publish in International Archives of Medicine

International Archives of Medicine is an open access journal publishing articles encompassing all aspects of medical science and clinical practice. IAM is considered a megajournal with independent sections on all areas of medicine. IAM is a really international journal with authors and board members from all around the world. The journal is widely indexed and classified Q1 in category Medicine.